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E Joseph Gess
Burns Doane Swecker & Mathis
P O Box 1404
Alexandria, VA 22313-1404

EXAMINER	
POLANSKY, GREGG	
ART UNIT	**PAPER NUMBER**
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,035	CHARBIT ET AL.	
	Examiner	Art Unit	
	Gregg Polansky	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2008* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicants' response, filed 3/26/2008, to the Office Action mailed 8/02/2007 is acknowledged. Applicants canceled Claims 6-10 and 12-14, amended Claims 1 and 11, and presented arguments in response to the Office Action.

2. Claims 1-5 and 11 are pending and presently under consideration.

3. Applicants' arguments have been fully considered and are persuasive in part. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Drawings

4. Replacement drawings included with Applicants' response, filed 3/26/2008 are not acceptable. The drawings are objected to because the text in the figures is in French and not English. This was not corrected as Applicants indicate in their response. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate

changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

5. 35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms that are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification are: "efficient" (*see* page 1, line 4), "dispose" (*see* page 3, lines 18 and 27), "antalgic" (*see* page 4, line 9), and "posology" (*see* page 14, line 29).

This objection is maintained from the previous Office Action since Applicants have failed to amend the Specification accordingly.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, because the Specification, while being enabling for treating transplant rejection, does not reasonably provide enablement for preventing transplant rejection. The Specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to the treatment and prevention of transplant rejection in humans and other animals.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Benfield ("Repeated Transplant Rejection: Why Does It Happen?") teaches the use of various immunosuppressant agents has reduced the rate of transplant rejection and improved the one-year survival of transplant patients. See 5th paragraph, page 1 and last paragraph bridging pages 1-2. However, the complete prevention of transplant rejection has not been achieved.

(5) The relative skill of those in the art:

The relative skill of those in the art is that of a medical doctor specializing in transplantation.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance and working examples for treating transplant rejection. For example, see pages 9-10 of the Specification. However, the specification does not provide a method for preventing transplant rejection. Figures 10-12, as described on pages 9-11 present data alleging to show a diacerhein related, dose-dependant reduction of tissue damage in a

mouse model of transplant rejection. However, the data do not demonstrate prevention of transplant rejection.

(8) The quantity of experimentation necessary:

The Office maintains a very high standard of enablement for claims drawn to a method of prevention. Considering the state of the art as discussed by the reference above, and the lack of guidance provided in the specification, one of skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Claim Rejections - 35 USC § 102

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Moore et al. (Osteoarthritis and Cartilage, Vol. 6, pages 19-23) (provided by Applicants).

Moore et al teaches diacerhein inhibits granuloma induced cartilage breakdown in rat femoral cartilage subcutaneously implanted (i.e., transplanted) in mice. The doses of diacerhein administered to the mice were 5, 15, or 50 mg/kg, administered orally. See "Summary", page 19 and last paragraph, page 23.

Moore et al. do not teach rhein or rhein derivatives increasing the levels of a heme oxygenase enzyme. However, it is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions

that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). **In the instant invention, the applicants must show that the teachings of Moore et al. do not work through the instant invention mechanism of up-regulation of a heme oxygenase enzyme.** There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

As required by instant claim 4, the determination of optimal dosage ranges is well within the purview of those skilled in the art through no more than routine experimentation. It is not inventive to discover the optimum or workable ranges by routine experimentation when general conditions of a claim are disclosed in the prior art. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233,235 (CCPA 1955) and MPEP 2144.05(11).

Claim Rejections - 35 USC § 103

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. Claims 1-5 and 11 are rejected under 35 U.S.C. 103(a) over Charbit et al. (U.S. Patent No. 6610750), in view of in view of Häyry (Abstract).

Charbit et al. teach a method of treating osteoarthritis, an inflammatory disease or condition, or an autoimmune disease, by the administration of diacerein, rhein and derivatives of rhein, at a dose of 25-500 mg/day (*see* column 7, 3rd paragraph, and claims 1-5). Oral administration of unitary doses of between 20 and 50 mg of diacerein is disclosed in column 6, lines 34-41.

Charbit et al. do not teach rhein or rhein derivatives increasing the levels of a heme oxygenase enzyme. However, it is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). **In the instant invention, the applicants must show that the teachings of Charbit et al. (i.e., treating osteoarthritis, inflammatory diseases/conditions or autoimmune diseases with rhein or diacerein) do not work through the instant invention mechanism of up-regulation of a heme oxygenase enzyme.** There is no requirement that a person of ordinary skill in the art would have

recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

Häyry teaches that "the etiology of chronic [allograft] rejection is most probably multifactorial" and that "the common feature in all organ allografts undergoing chronic rejections is persistent perivascular inflammation…".

One of ordinary skill has good reason to pursue the known options within his or her technical grasp, therefore it would have been obvious to try to treat organ rejection by taking advantage of the anti-inflammatory properties of diacerein. Seeking a method of treating transplant rejection would have been further motivation to combine the teachings of Charbit et al. and Häyry.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the

claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claims 1-5 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moore et al. (Osteoarthritis and Cartilage, Vol. 6, pages 19-23) (provided by Applicants), in view of Charbit et al. (U.S. Patent No. 6610750).

The teachings of Moore et al. and Charbit et al. are presented *supra*.

Moore et al. does not teach the unitary doses required by instant Claim 11. As presented *supra*, Charbit et al. teach unitary doses of between 20 and 50 mg of diacerein.

It would have been obvious to one of ordinary skill at the time of the invention to utilize the unitary doses taught by Charbit et al. in combination with the teachings of Moore et al. One would have been motivated to treat transplant rejection with diacerhein as taught by Moore et al. and suggested by Charbit et al., with the unitary doses taught by Charbit et al. Because both references teach the oral administration of diacerhein for the treatment of conditions which read on the instantly claimed invention.

Conclusion

12. Claims 1-5 and 11 are rejected.

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1611

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614